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EDITORIAL COMMENT

Having It Both Ways*

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No fail-safe method can determine which patients with acute coronary syndromes (ACS) will stabilize on medical therapy alone or require early angiography and percutaneous coronary intervention (PCI). Troponin elevation, one of the strongest predictors of the presence of coronary artery disease in risk models of ACS (1), frequently triggers an immediate invasive evaluation. But the effect of early angiography on late mortality has been mixed (1). As a result, 2 contrasting, but not totally exclusive approaches have emerged for the management of patients with ACS: a routine early invasive strategy and a delayed selective invasive strategy.

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In this issue of the *Journal*, Damman et al. (2) present the 5-year follow-up of the ICTUS (Invasive versus Conservative Treatment in Unstable coronary Syndromes) trial. In the original report (3), patients with non–ST-segment elevation myocardial infarction (NSTEMI) assigned to the early invasive strategy within 24 to 48 h were as likely as those randomized to conservative management to experience the primary outcome of death, myocardial infarction (MI), or rehospitalization for angina within 1 year (22.7% vs. 21.2%). All patients in the ICTUS study had an elevated troponin T level, but the early invasive strategy did not confer a better outcome in the presence of additional high-risk features such as advanced age, ST-segment depression, or a high level of troponin T (3). The 3-year follow-up study (4) also reported similar rates for the combined primary end point for both strategies (30.0% vs. 26.0%). Because of the possibility of late attrition in the conservatively managed patients, the 5-year follow-up was completed and reported here (2).

Equipoise. The current report (2) describes similar 5-year cumulative event rates for the composite end point of death or spontaneous MI for the routine invasive and selective invasive groups (17.5% vs. 16.1%). Trends for other end points were suggested, but no conclusive differences appeared between the early versus selective invasive strategies in the rates of spontaneous MI (8.6% vs. 9.4%), all-cause mortality (11.1% vs. 9.9%), or cardiovascular death (6.5% vs. 6.8%). Of note, no significant differences between the 2 approaches emerged across a broad range of risk scores, and there was no late-mortality effect (2).

Although the ICTUS study was originally designed to contrast 2 strategies that differed in the timing and use of invasive procedures (2), most patients in both groups had undergone angiography during the initial hospitalization, during which 76% in the early invasive group and 40% in the selective invasive group had also required revascularization (3). During the 5 years of observation, the majority of patients in both groups ultimately underwent PCI or bypass surgery (81% vs. 60%) (2).

Drawbacks of the early invasive strategy. A greater number of periprocedural MIs was the major limitation of the early invasive strategy in the ICTUS trial (3). The finding was consistent across a range of definitions, which altered the absolute, but not the relative, rates of ischemic events between the 2 strategies (3). An ascertainment bias against the early invasive group may have emerged during follow-up, however, because of the nonsystematic collection of data for periprocedural MIs after 3 years (2).

New information about the prognostic implications of periprocedural MIs continues to appear in the contemporary literature. A recent study from the Mayo Clinic registry has suggested that spontaneous pre-procedural troponin elevation independently predicted death over a median follow-up of 28 months (hazard ratio [HR]: 1.8, 95% confidence interval [CI]: 1.4 to 2.4), but the occurrence of procedural-related myonecrosis did not (5). An analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial has found that spontaneous MIs unrelated to PCI were strong independent predictors of 1-year mortality (HR: 7.5, 95% CI: 5.0 to 11.3), whereas procedure-related MIs were not (6). In the ICTUS trial, the early invasive approach resulted in more post-procedural ischemic events than the delayed selective strategy but was not associated with increased cardiovascular mortality or spontaneous MIs during long-term follow-up (2).

Drawbacks of the delayed selective invasive strategy. As compared with the early invasive strategy, prolonged hospitalization until PCI (1 day vs. 11 days) and higher rates of rehospitalization (7.4% vs. 10.9%) initially appeared to be drawbacks of the delayed selective invasive strategy (3). The 3-year ICTUS report (4) clarified that the initial hospital stays were similar for patients assigned to the 2 strategies (6 days vs. 7 days, respectively), but these lengths of stay were notably longer than the hospitalizations in contemporary trials comparing early versus delayed intervention for ACS (2 days vs. 3 days, $p < 0.001$) (7).

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The timing of an invasive evaluation for NSTEMI. The results of ICTUS extend the findings from 2 current studies (7,8) and suggest that the timing of invasive evaluation can be flexible for most patients with NSTEMI. In many health care settings, however, concerns about long hospital stays or the discharge of high-risk patients without an invasive evaluation (8) may limit the broad application of the delayed selective strategy. Despite the caveats, many strengths of the ICTUS trial have clinical relevance. As a strategy-based trial, ICTUS allowed physicians caring for patients to adjust therapy as they might in practice, making the outcome applicable to the everyday care of patients with NSTEMI and providing reassurance that a selective invasive approach is an acceptable alternative to an early invasive strategy for different clinical scenarios. This means, for instance, that patients with active bleeding and NSTEMI could defer angiographic evaluation without incurring additional risk, and that low- or moderate-risk patients who stabilize on medical therapy can be managed conservatively and undergo semi-elective invasive evaluation should stress testing show evidence of ischemia.

Regardless of the angiographic strategy ultimately selected for patients with NSTEMI, medical therapy should include the early use of aspirin, a thienopyridine, an antithrombin, beta blockade, statin therapy, intravenous nitroglycerin, and probably an angiotensin-converting enzyme (ACE) inhibitor. Platelet-glycoprotein IIb/IIIa inhibitors may not be required during initial medical management (9). The early use of clopidogrel seems appropriate (10) because <8% of patients with ACS require urgent bypass surgery in contemporary practice (11).

Remaining questions and challenges. The results of the ICTUS trial suggest that patients with NSTEMI who stabilize on medical therapy can safely wait for an invasive evaluation (2). But the question remains: Is it *worth* the wait? In other words, do patients who wait for angiography have equally good outcomes and levels of satisfaction as those managed with upfront angiography?

Until further research is completed, a dualistic approach will dominate the management of ACS. All patients with NSTEMI will require intensive medical therapy, and almost all patients will undergo invasive procedures. Angiographic approaches will prevail because the "plumbing model" of coronary artery disease comes up in bedside discussions of ACS more often than the new paradigm of endothelial dysfunction, arterial inflammation, and plaque rupture (12). In the new era of comparative effectiveness research, however, cost and quality metrics will be measured alongside hard clinical outcomes to ultimately define how various strategies reduce resource utilization and achieve optimal benefits for patients with NSTEMI.

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